REMARKS

No amendments have been made to the previously pending claims in this response. New Claims 58-59 have been added. Thus, Claims 1-5, 29-37 and 38-59 are pending in the application, with Claims 1, 42, 58 and 59 being the only independent claims. Claim 53 has been canceled without prejudice or disclaimer. Support for the new claims is found throughout the specification as originally filed. More particularly, support for new Claim 59 is found, *inter alia*, in Tables 3-7 of the specification. No new matter has been added with the foregoing amendment and newly added claims. Reconsideration is respectfully requested.

Objected to Claim 53 and Allowable Subject Matter

The Examiner objected to Claim 53 as being dependent upon a rejected base claim, but stated that Claim 53 would be allowable if rewritten in independent form to include all of the limitations of the base claim and any intervening claims.

Applicants have added new Claim 58, which includes the subject matter of Claim 53 rewritten in independent form to include all of the limitations of base Claim 42.

Accordingly, Applicants respectfully request that new Claim 58 be allowed.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 54 was rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. According to the Office Action, Claim 54 lacks antecedent basis for the phrase "said first antigen and said second antigen are the same" because base Claim 42 recites that the antigens are different. Applicants respectfully traverse the indefiniteness rejection.

Claim 54 depends from independent Claim 42. Respectfully, the objected to language in Claim 54 has antecedent basis in Claim 42. Independent Claim 42 recites, *inter alia*, "a first antigen associated with a first target cell" and "a second antigen associated with a second target cell." Contrary to what is stated in the Office Action, Claim 42 does ***not*** recite that the antigens are different. While Claim 42 recites that the first and second ***housekeeping epitopes*** are not the same, Claim 42 leaves open the possibility that the first and second antigens are the same or different. That is consistent with the understanding in the art that two separate target cells, for example tumor cells, can express the same antigen and/or different antigens. Therefore, the

phrase in Claim 54 reciting that "said first antigen and said second antigen are the same" has proper antecedent basis, and Applicants respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 102

Zajac et al.

Claims 1-5, 29, 30, 33-35, 38-52 and 55-57 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Zajac *et al.*, *Int. J. Cancer* 1997 71:491-496 ("Zajac *et al.*"). The Examiner alleges that Zajac *et al.* teach a composition comprising T cells that recognize the HLA-A2.1-restricted housekeeping epitope consisting of amino acid residues 27-35 of the Melan-A antigen. Applicants respectfully submit that Zajac *et al.* do not anticipate the claims at least because they do not disclose, teach or suggest all the limitations of the claims.

A. Claims 1-5, 29, 30, 33-35 and 38-41

The subject matter of Claims 1-5, 29, 30, 33-35 and 38-41 relates to compositions which are suitable for adoptive administration to a human. The claimed compositions comprise an isolated T cell expressing a T cell receptor specific for an MHC-peptide complex comprising a housekeeping epitope. Independent Claim 1 explicitly recites that the claimed composition is suitable for adoptive administration to a human. As such, the compositions of the claimed subject matter are necessarily suitable for adoptive administration to a human.

Zajac *et al.* discussed generation of tumoricidal lymphocytes from healthy donors after *in vitro* stimulation with a replication-incompetent *Vaccinia* virus encoding MART-1/Melan-A 27-35 epitope. Zajac *et al.* did not disclose or mention the use of T cells for adoptive administration to a human. Specifically, Zajac *et al.* disclose the generation of T cells after *in vitro* stimulation with a replication-incompetent *Vaccinia* virus encoding MART-1/Melan-A 27-35 epitope (*see*, Abstract, Zajac *et al.*). However, in stark contrast to the presently claimed subject matter, Zajac *et al.* do not teach compositions comprising T cells for adoptive administration to a human. The Examiner has previously acknowledged that the T cells ultimately derived and disclosed by Zajac *et al.* are not suitable for adoptive administration to a human because, during generation of MART-1/Melan-A_{27-35}-specific CTLs, Zajac *et al.* exposed the T cells to agents which rendered the compositions unsuitable for adoptive administration to a human.

The Examiner alleges that "prior to transformation of the cell line the reactive T cells were present in human serum, a carrier suitable for administration to a human. The composition satisfies the metes and bounds of the claims." Applicants respectfully disagree, and assert that Zajac *et al.* do not anticipate the subject matter of the rejected claims because, for example, the initial T cell populations do not exhibit any detectable reactivity against the MART-1/Melan-A_{27-35} peptide.

As discussed above, the Zajac *et al.* publication relates to the ***generation*** of tumoricidal lymphocytes from healthy donors ***after*** *in vitro* stimulation with a replication-incompetent *Vaccinia* virus encoding MART-1/Melan-A 27-35 epitope. According to Zajac *et al.*, "no cytotoxic activity specific for the MART-1/Melan-A_{27-35} peptide was detectable in any culture before initiation of the CTL induction experiments." *See*, page 493, col. 1, Zajac *et al.* Thus, in contrast to the subject matter of the rejected claims, and contrary to what is stated at page 3, lines 4-6 of the Office Action, the initial T cell populations did ***not*** exhibit any detectable specificity against the MART-1/Melan-A_{27-35} peptide.

Moreover, the compositions used in generating MART-1/Melan-A_{27-35}-specific CTLs by Zajac *et al.* contained antibiotics and 10 units/ml recombinant human IL-2. The addition of the antibiotics and IL-2 rendered these compositions unsuitable for administration to a human. Applicants assert one of skill in the art would recognize that none of these agents are acceptable components of a composition to be administered to a human or an animal because of expected toxicity and/or allergic reactions in response to such agents. Zajac *et al.* do ***not*** teach or suggest isolating or purifying the MART-1/Melan-A_{27-35}-specific CTLs from the culture medium. Therefore, Zajac *et al.* do ***not*** teach compositions which are suitable for adoptive administration to a human comprising an isolated T cell expressing a T cell receptor specific for an MHC-peptide complex comprising a housekeeping epitope. As such, Zajac *et al.* do not anticipate the subject matter of Claims 1-5, 29, 30, 33-35 and 38-41. Applicants respectfully request withdrawal of the rejection.

B. Claims 42-52 and 55-57

The subject matter of Claims 42-52 and 55-57 relates to a composition comprising at least a first and a second isolated T cell population, wherein the first and second T cell populations recognize two different housekeeping epitopes. Independent Claim 42 recites that

the T cell populations expresses a T cell receptor specific for an MHC-peptide complex comprising a housekeeping epitope, and that housekeeping epitopes of the first T cell population is not the same as the housekeeping epitope for the second T cell population. Thus, the T cell populations recited in Claim 42 exhibit specificity for two distinct housekeeping epitopes.

In stark contrast to the subject matter of Claims 42-52 and 55-57, Zajac *et al.* disclose a T cell population that exhibits cytotoxic activity specific for a single epitope, MART-1/Melan-A_{27-35} (*see*, Zajac *et al.* at, for example, page 493, col. 1). At no point do Zajac *et al.* teach or suggest a composition comprising at least two isolated T cell populations wherein the T cell populations exhibit cytotoxic activity specific for two different housekeeping epitopes.

Furthermore, the subject matter of the instant claims relates to compositions which are suitable for adoptive administration to an animal. The claimed compositions comprise an isolated T cell expressing a T cell receptor specific for an MHC-peptide complex comprising a housekeeping epitope. Independent Claim 42 explicitly recites that the claimed composition is suitable for adoptive administration to an animal. As such, the compositions of the claimed subject matter are necessarily suitable for adoptive administration to an animal. Applicants assert, for at least the reasons discussed above regarding the unsuitability of the Zajac *et al.* compositions for adoptive administration to a human, that the compositions comprising MART-1/Melan-A_{27-35}–specific CTLs disclosed by Zajac *et al.* are ***not*** suitable for adoptive administration to an animal. In addition, the compositions disclosed by Zajac *et al.* contain cells which are human in origin. One of skill in the art would recognize that a non-human animal's immune system would react against and destroy human cells administered to the animal. Thus, compositions comprising human cells are not suitable for adoptive administration to any non-human animal.

For at least the reasons discussed above, Zajac *et al.* do not anticipate the subject matter of Claims 42-52 and 55-57. Applicants respectfully request withdrawal of the rejection.

Kittlesen et al.

Claims 1-5, 29, 30, 33, 34, 36 and 38-41 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kittlesen *et al.*, *J. Immunol.* 1998 160:2099-2106 ("Kittlesen *et al.*"). The Examiner alleges that Kittlesen *et al.* teach isolated T cells lines that recognize the epitope consisting of the amino acid sequence KCDICTDEY of tyrosinase tumor-associated antigen

from melanoma target cells. Applicants respectfully submit that Kittlesen *et al.* do not anticipate the claims at least because they do not disclose, teach or suggest all the limitations of the claims.

As discussed above, the subject matter of Claims 1-5, 29, 30, 33, 34, 36 and 38-41 relates to compositions which are suitable for adoptive administration to a human comprising an isolated T cell expressing a T cell receptor specific for an MHC-peptide complex comprising a housekeeping epitope. Independent Claim 1 further recites that the composition comprises a pharmaceutically acceptable carrier, adjuvant, diluent, or excipient.

Kittlesen *et al.* discussed recognition by human melanoma patients of an HLA-A1-restricted epitope from tyrosinase containing two cysteine residues. Kittlesen *et al.* did not disclose or mention the use of T cells for adoptive administration to a human. Particularly, Kittlesen *et al.* disclose screening of human melanoma patient CTL lines expressing HLA-A1 for reactivity against various melanocyte differentiation proteins, including tyrosinase. Kittlesen *et al.* disclose CTLs derived from peripheral blood lymphocytes, tumor-involved nodes, or tumor-draining nodes cultured *in vitro* and repeatedly stimulated with autologous tumor cells. *See*, page 2100, col. 1, Kittlesen *et al.* The cells were cultured in medium with fetal calf serum, glutamine, and antibiotics.

In stark contrast to the presently claimed compositions, the CTL compositions disclosed by Kittlesen *et al.* are not suitable for adoptive administration to a human. The presence of antibiotics in the medium used to culture CTLs generated by Kittlesen *et al.* to exhibit antigen specificity renders the disclosed compositions unsuitable for adoptive administration to a human. Applicants assert one of skill in the art would recognize that antibiotics are not acceptable components of a composition to be administered to a human or an animal because of expected allergic reactions. Kittlesen *et al.* do ***not*** teach or suggest isolating or purifying the CTLs from the culture medium.

The Examiner asserts that Kittlesen *et al.* teaches compositions of reactive T cells suitable for administration to a human because "Kittlesen teaches that the tyrosine reactive T cells are obtained from melanoma patients whose tumors express tyrosinase." *See*, page 3 of the Office Action. According to the Examiner, prior to establishment of the cell line, the T cells present in human serum constitute a composition suitable for administration to a human. However, contrary to what is stated in the Office Action, at no point do Kittlesen *et al.* teach or suggest compositions comprising isolated, reactive T cells present in human serum only.

Kittlesen *et al.* only teach that the melanoma cell lines VMM12, VMM14 and VMM15, and the fresh tumor cell digests VMM21 and VMM40 were obtained from melanoma patients, and that the tissue culture medium used for the human cell lines was RPMI 1640 supplemented with 10% FCS, glutamine, and antibiotics (*see*, Kittlesen *et al.*, page 2100, first paragraph of the Materials and Methods section). One of skill in the art would recognize that untested, unpurified and untreated cells taken directly from melanoma patients would ***not*** comprise a composition suitable for adoptive administration to a human. Administration of such a composition would be undesirable because it would entail a high risk of inoculating the human recipient with tumor cells likely to be present in the composition.

For at least the reasons discussed above, Kittlesen *et al.* do ***not*** teach compositions which are suitable for adoptive administration to a human comprising an isolated T cell expressing a T cell receptor specific for an MHC-peptide complex comprising a housekeeping epitope. Thus, Applicants respectfully request withdrawal of the rejection because Kittlesen *et al.* do not anticipate the subject matter of the rejected claims.

Jager et al.

Claims 1-5, 29-32, 35 and 38-41 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Jager *et al.*, *J. Exp. Med.* 1998 187:265-270 ("Jager *et al.*"). The Examiner alleges that Jager *et al.* teach isolated CD4+ T cell lines and an HLA-A2 restricted CTL clonal line that recognize housekeeping epitopes. Applicants respectfully submit that Jager *et al.* do not anticipate the claimed subject matter at least because they do not disclose, teach or suggest all the limitations of the claims.

As discussed above, the subject matter of Claims 1-5, 29-32, 35 and 38-41 relates to compositions which are suitable for adoptive administration to a human comprising an isolated T cell expressing a T cell receptor specific for an MHC-peptide complex comprising a housekeeping epitope.

Jager *et al.* discussed the antigen-specific humoral and cellular immune responses against human tumor antigens. Jager *et al.* did not disclose or mention the use of T cells for adoptive administration to a human. Specifically, Jager *et al.* disclose the generation of CTLs which exhibit antigen specificity by culturing autologous peripheral blood lymphocytes (PBL) with a tumor cell line established from a malignant melanoma patient.

According to the Office Action, "Jager teaches that the NY-ESO-1 reactive T cells are obtained from PBL and a needle biopsy from a melanoma patient. Jager teaches that the NY-ESO-1 reactive T cells are obtained from a melanoma patient and therefore qualify as being 'isolated from an immunized animal.'" Applicants respectfully disagree. The cells obtained by needle biopsy were used "to confirm the diagnosis of melanoma and to establish the ***tumor*** cell line NW-MEL-38." *See*, Jager *et al.*, page 266, col. 1, Material and Methods, *Patient*. Clearly, the cells obtained from the biopsy referred to in the Office Action were ***tumor*** cells, ***not*** reactive T cells.

To obtain the stable CTL line NW38-IVS-1, Jager *et al.* cultured mixed lymphocyte tumor cell cultures of PBLs and the autologous tumor cell line from patient NW38. *See*, page 266, col. 1, last sentence bridging to col. 2, Jager *et al.* Jager *et al.* disclose that the cells were cultured in medium containing antibiotics. The presence of antibiotics in the medium used to culture CTLs renders the CTL composition unsuitable for adoptive administration to a human. Applicants assert one of skill in the art would recognize that antibiotics are not acceptable components of a composition to be administered to a human because of expected allergic reactions. Jager *et al.* do ***not*** teach or suggest isolating or purifying the CTLs from the culture medium.

The Examiner alleges that prior to transformation of the cell line the reactive T cells were present in human serum and thus comprised a composition suitable for administration to a human. *See*, page 4 of the Office Action. Applicants respectfully disagree. Jager *et al.* do not disclose isolated reactive T cells in human serum other than possibly suggesting that reactive human T cells are present in whole blood in melanoma patients. One of skill in the art would recognize that untested, unpurified and untreated cells taken directly from a melanoma patient would ***not*** comprise a composition suitable for adoptive administration to a human. Administration of such a composition would be undesirable because it would entail a high risk of inoculating the human recipient with tumor cells likely to be present in the composition.

Thus, contrary to what is stated in the Office Action page 4, the composition prior to transformation of the cell line does not satisfy the metes and bounds of the claims. As such, Jager *et al.* do ***not*** teach compositions which are suitable for adoptive administration to a human comprising an isolated T cell expressing a T cell receptor specific for an MHC-peptide complex

comprising a housekeeping epitope. As such, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 3-5-06

By: _____

Susan L. Wang
Registration No. 53,742
Attorney of Record
Customer No. 20,995
(415) 954-4114

3490727
030207